

Pharmaceutical Custom Manufacturing – Offering challenges

1. The pharma industry environment

Custom manufacturing is intimately linked to developments in the pharmaceutical industry and a brief summary of trends in the pharma industry and drivers for change in this industry is given first.

• **Increasing cost of R&D, Productivity issue**

Over the past years total R&D spending in the pharmaceutical industry has steadily and continuously gone up to over 200 bio. \$ in 2001. On the other hand the number of NCE's (New Chemical Entities) approved/launched per year has gone down from more than fifty a few years ago to less than thirty in the most recent years. At the same time it is estimated that the cost of bringing an NCE to the market is now in excess of 800 mio. \$ to a pharmaceutical company with approx. 75% accounting for attrition – the pharma industry is suffering from a lack of innovation due to its failing R&D.

The biggest companies are now concentrating their resources on blockbuster medicines, which are defined as products with an annual sales potential of \$1 billion or more. Blockbusters generally deliver a faster return on a company's R&D investment than a succession of smaller products. But by focussing on blockbusters, are companies being driven more by financial than by public health considerations? The fall in applications may also reflect changes in the marketplace which is now characterised by very big and very small companies. Medium-sized companies are being squeezed out with the result that fewer "me-too" products are being developed. There has clearly been a reduction in competition in this sense.

• **Tougher political and regulatory environment**

A transitory lack of FDA leadership and the ever growing raise in Health Care costs have and do impact the pharmaceutical industry. Equally important is the burden imposed on pharma companies to bring a new product to the market – in today's environment more trials are requested. These trials tend to be larger (patients) and drug/drug interactions need to be considered. In 1987 the costs associated with bringing a new product to the market was estimated to be 231 mio.\$ - taking only inflation into account this number should have become 318 mio.\$ in 2000. The actual number was however 802 mio.\$ as stated above.

• **Profit warnings – generic exposure – industry margin deterioration**

Over the last two years Pharma companies have suffered sustained multiple contraction as concerns grow among investors about the quality of earnings going forward.

The earnings outlook is significantly lower for European and US Pharma companies than recent earnings performance.

There has been a marked increase in the number of profit warnings from Pharma companies over the past 12 months.

Big Pharma companies are confronted with a huge and significant threat of revenue losses due to patent expiration. These revenue losses are not the same across the industry but in the timeframe 2002-2006 they may affect current sales levels by as much as 56% (Schering-Plough), 40% (Sanofi-Synthelabo), 35% (Pfizer), 34% (BristolMyers-Squibb) Or 33% (Takeda).

A study published by Datamonitor a year ago about innovative strategies to overcome industry margin deterioration has come to the following main observations/conclusions :

1) There are no significant economies of scale in sales activities for the Pharma companies being analysed in this study. The revenues of pharmaceutical companies tend to be proportional to their sales, general and administration spend. Considering the US companies it appears that ethical revenues are linear to the number of US sales representatives. In other words increasing the number of representatives or the expenses on sales operations will only result in higher turnover but not margin growth. In fact the average sales representative call with a doctor now lasts less than five minutes. Representatives are often promoting drugs whose comparative merits take some time to explain. Again as per a Datamonitor study for every dollar spent on marketing (not exclusively by representatives), the industry's top 14 firms earned an average of only 17\$ in sales in 2001, down from \$22 in 1998.

2) A similar conclusion can be drawn from R&D investment: no significant economies of R&D investment could be identified. The value of a pharma company's pipeline in 2001 is directly proportional to its R&D spend in 1998.

3) Size as such is not an advantage in creating value for Big Pharma.

2. Collaborations/partnerships between biotech and big Pharma

In order to overcome the innovation gap and to try and meet the investors expectations big Pharma houses can act on increasing sales (marketing, see above), reducing costs or divesting assets. In order to get access to new products big Pharma companies are increasingly cooperating or partnering with small biotech companies or eventually purchasing them – increasing R&D costs and fewer New Molecular Entities (NMEs) are drivers of recent megadeals.

Biotech is typically

Highly Innovative
Risk Taking
Rapidly Evolving

FIPCO potential Platform to Product

whereas **Big Pharma** can be characterised by

Innovative but Risk Averse
Highly Capable
Pipeline is Lifeblood
Commercial Powerhouse
Global Player

Interactions between small Biotech and big Pharma can obviously take place at the level of technologies, capabilities and/or products – it can vary between acquiring a technology platform to a late-stage product in development.

The following observations are characteristic of the current situation in the pharmaceutical industry:

→ Over half of today's top 20 prescription drugs are associated with significant collaborations of various kinds in the industry.

→ Strategic alliances between biopharma companies have become increasingly prevalent over the last decade.

→ Today large pharma companies tend to have an equal share of drugs developed in-house and in-licensed.

An interesting and obviously important question for big Pharma houses is obviously how to deal with their own developments at the same time as with the in-licensed compounds. In general very little is known about the attractiveness of both these activities within big Pharma. One of the few published studies was conducted in 2000 by the university of Siena in Italy. Success rates of licensed versus in-house drug compounds for the top 100 pharmaceutical companies were compared for the various stages of clinical development. Interestingly enough the success rates (measured as likelihood of advancing from one stage to the following one) were better for licensed products in all stages – in phase II/III clinical phase the success rate for licensed products was 85.7% as opposed to 62.0% for in-house developed products. Although it is difficult to interpret this finding one reason may well be that in-licensed compounds have stronger or more determined project managers within big Pharma.

→ At the same time deal making is becoming increasingly competitive. As the industry has recognized the need to partner both licensing expenditures and the number of competitors for a given licensing deal are rising.

→ Early stage alliances are becoming more frequent – they tend to be concluded more and more often for discovery projects rather than preclinical/phase I or Phases II/III projects.

3. Platform Technologies / Drug discovery and development

The platform technologies have escalated over the last decade:

Early '90's: Combinatorial Chemistry
Mid – '90's: Genomics
Pharmacogenomics
Late '90's: Proteomics
Validation Technologies

What does it mean and where can we expect to go from here?

The mechanistic basis of some diseases is now well understood and therapeutics targets are refined (cholesterol lowering or essential hypertension), some diseases are at an emerging stage of knowledge and other diseases are largely unexplained (schizophrenia and depression).

Will there be further blockbusters or rather personalised medicine?

Generally it is felt that both are not mutually exclusive. Some conditions like cancer in particular lend themselves to a gene-chip based personalised approach. Others like essential hypertension as an example are likely to be treated in the future much as now but with a more individualised approach for those not responding to standard therapy. Another statement by Dr. Francis Collins, director of the National Human Genome Research Institute at the NIH: " By 2010 predictive tests for around 25 conditions are likely to become available. By 2020 gene-based designer drugs for diabetes, hypertension and other complex diseases will be coming onto the market."

It will be essential for drug development that diagnosis and therapy get more closely associated.

Even with all the technologies available today drug discovery and development is still about increasing the probability of success. Drug discovery is not an exact science. There is a need to increase the "number of shots on goal" by increasing the diversity of chemical libraries, improve screening throughput and precision and better validate biological targets. Efforts will be focused in areas of true medical need (obesity / type II diabetes, Alzheimer's disease) and the **efficiency of the development process needs to be increased.**

Ideas and techniques are worth the same whether from inside or outside a pharmaceutical company.

The ability to pursue parallel approaches to drug-discovery problems have changed the business, providing growth opportunities to small biotechnology companies whose expertise and nimbleness are critical to the success of Big Pharma. Small companies continue to enter the post-genomics arena with niche innovative technologies for investing complex biological processes, accelerating the discovery and validation of targets, and developing new drugs and diagnostics. The majority of these technology companies have fewer than 300 employees.

Genomics are not a replacement to current methodologies but rather an extension enabling the generation of more information. The genomics strategy is to

- accelerate incorporation of genomic era technologies into drug discovery programs
- establish genomic analyses in preclinical and safety assessment programs

- utilize genomic information as integral part of clinical drug development

What drug candidates will result from this hopefully but yet to be confirmed more efficient drug development process? The number of biotech drug candidates is up as is the number of approvals of biotech products and the number of biotech product launches.

Primary growth in the ethical drug market will be driven by biopharmaceuticals frequently discovered by smaller companies and developed with larger partners.

4. Custom manufacturing of small molecules (chemical manufacture)

Several factors have dampened the once-rosy outlook for pharmaceutical fine chemicals:

That was then.....

"The fine chemical/pharmaceutical contract manufacturing industry will grow in excess of 15% per year over the next five years"

Deutsche Bank (Sep 1999)

"The current growth in fine chemicals is the largest opportunity I have seen in specialty chemicals in my years in the industry"

S. Hannman, CEO, BTP (Nov 1999)

.....this is now

"Rough times facing fine chemicals...such as pharmaceutical custom synthesis appear to be particularly hard hit, contrary to earlier forecasts predicting continuing profitable growth"

E. Polastro, ADL (in CMR Aug 2002)

"We are optimising, restructuring, selling or closing some of our sites in LSE in addition to streamlining our product- and project-portfolio"

R. Handte, CEO, Clariant (June 2002)

Issues facing Fine Chemicals / Contract Manufacturing Suppliers are

► Decrease in the number of new chemical entities (NCE) being approved (ca. 20 in 2002 versus over 50 in 1997 – increasing number of biotech derived products)

► Withdrawal and delay of new pharmaceutical products. A number of potentially large products have been delayed or withdrawn in late stage clinical trials (Crestor/Vanlev/Iressa, etc). A significant number of products had to be withdrawn

from the market in the past years. Major delays associated with additional indications/markets create significant forecast issues (COX-2 class, Vaniqa-eflornithine, Proscar/Propecia-finasteride).

A number of launched products are facing softer than expected demand, like the anti-influenza drugs Tamiflu (Roche) and Relenza (GSK), the HIV drug Abacavir (GSK) or the anti-obesity drug Xenical (Roche)

► Decreased demand for outsourcing from pharmaceutical companies as product pipelines have decreased and mergers have increased idle internal capacity.

However:

some companies like Merck, Pfizer, Abbott or Lilly are expected to maintain manufacturing as a core competency.

there is continued growth and investment by many big Pharma houses

- Ireland investments: Pfizer/Merck/BMS/GSK
- UK/US investments: Novartis, Roche
- Singapore growth: SP/Merck/Pfizer/GSK/Lilly

► Competition from the Far East

New companies like Dr. Reddy's, Ranbaxy, Auribindo, Hetero, Cipla, Wockhardt, Dishman, Divi, Orchid, Hikal, Biocon, Scinopharm

► Overcapacity has resulted

Pharmaceutical companies are using internal assets for manufacturing to improve their bottom line

In-house synthesis capabilities run at 50 – 70% of capacity

Fine chemical players operate at only slightly better utilisation

► Prices and profitability have declined

Return on Net Operating Assets (RONOA) has declined from close to 20% 5 years ago to approx. 10% in 2001.

Public Market Perspective

"Globally the market for exclusive synthesis products is witnessing significant over capacity...in-sourcing of production back to pharma houses has continued...This combined with the lower number of new product approvals and launches have resulted in a stagnating market for custom manufacturing through 2001. We believe growth in classical pharma intermediates will be 0-3% in the coming two to three years"

Deutsche Bank 10/16/02

"The market remains tough for pharma intermediates and custom manufacturing due to a combination of factors including excess industry capacity, price pressures from pharma customers, and a slowdown in the rate of new drugs approvals"

Merrill Lynch 10/04/02

"The Fine Chemicals industry has been affected by a combination of patent expiries on pharmaceutical products, delays of new product launches and a slowing in the rate of outsourcing on the part of the pharmaceutical industry. Nevertheless, the trend towards outsourcing should continue, driven by the need to reduce costs and by the increased complexity of new AIs."

ABN Amro 07/03702

Offering challenges in the small molecule custom manufacture

Asset utilisation / asset optimisation – restructuring

Marketing / Pricing (margin erosion versus asset utilisation in times of overcapacity)

Involvement in earlier stage developments – risk taking / sharing

Involvement in generics manufacturing – a way of balancing the inherent volatility of the custom manufacturing market? Will there be a future for "non Far East" generic manufacture in the long run?

Project and Supply Chain Management services during the whole product life cycle – development of new supply chain understanding

Extend customer base (from big Pharma to medium-size and small companies) – big Pharma accounts for an estimated 40% share of the total outsourcing market

Extend technology base (peptides, oligonucleotides, microreactions,,,,,)

Manufacturing rights with increasing number of collaborations/partnerships ? – small companies may not be willing to guarantee manufacturing rights for a jointly developed project in order to be open for as many options as possible in a licensing deal

Process development bottleneck for genomics/proteomics potential ?

Strategic collaborations / new business concepts and value propositions for the pharmaceutical industry to be worked out.

5. Custom manufacturing of biopharmaceutical molecules (mammalian and microbial fermentation)

Several ten years of investment in biotechnology have fueled a market expected to grow from \$20 billion in 2001 to over \$35 billion by 2005. With over 300 large molecules currently in clinical development, biotechnology may well be the leading source of new products in 10 years from now. This is an exciting opportunity but a

challenge at the same time: how to ensure that enough product is manufactured to meet the demand.

Anticipated market growth

(source: various industry surveys, in.house research)

- ◆ Therapeutic protein market is expected to grow approx. 15% p.a.
- ◆ Mammalian cell culture contract manufacturing market will see growth of approx. 20% p.a.
estimated 200-400% capacity shortage in 2006
- ◆ Microbial cell culture contract manufacturing market is expected to grow approx. 15% p.a. from 1998 numbers
estimated 200% capacity shortage by 2006
- ◆ Transgenic animal contract manufacturing market to grow 10% p.a. to 2001, 15% p.a. to 2003 then 20% p.a. thereafter

Protein manufacturing characteristics

Large molecules cannot yet be as well characterized as small molecules. For this reason and in contrast to small molecules, in addition to the molecule itself, regulation of large molecules also focuses on the manufacturing process. The difficulty of changing a process and the expense eventually associated with it restrict the opportunity to optimize large molecule manufacturing processes. This situation, together with the development speed of humanized monoclonal antibodies and their high dosage required has led to a shortage in biomanufacturing capacities.

Even with the planned additions to manufacturing capacity a significant shortage of capacity is expected in mammalian cell culture in particular. This creates a situation in which biomanufacturers with available capacity will have leverage over those in need – seizing the most valuable opportunities while dealing with the risks is key.

Due to the complexity of the manufacturing processes and regulation, biomanufacturing decisions require longer lead times than for typical small molecules. The manufacturing strategy for large molecules must be determined early in the development process when attrition rates are still high.

In addition to the uncertainties inherent in the project itself possibilities of future overcapacity need to be considered as both custom manufacturers and pharmaceutical companies build new facilities. It is also possible that new technologies – highly productive new expression systems or perhaps transgenic plants – may make existing manufacturing processes obsolete.

Offering challenges in the biopharmaceutical custom manufacture

Strategic choices regarding capacity, technologies and capabilities – in which geographical areas will future investments make best sense ?

What technology platforms should be developed? Microbial fermentation, mammalian cell culture, or novel manufacturing platforms?

What capabilities are needed? Examples are process design and development technologies, purification technologies and downstream processing, sterile manufacturing capabilities.

Selection of target customers and the identification of projects to be pursued or rejected – relevant resource allocation and/or commitment. Different levels of support may include dedicated future capacity, development funding, and other potential forms of risk sharing.

As mammalian cell fermentation is developing very rapidly from the development mode into a manufacturing status it is key to ensure robust manufacture with a top manufacturing team.

Watching and assessing emerging technologies is crucial.

Human Resource activities are essential and critical in this evolving and strongly growing field.

Summary

The Pharma industry is going through a major change and it does present challenges to the custom manufacturing industry. There is no single solution to the challenges. There will be more consolidation in the chemical, small molecule arena and biotechnology is obviously emerging. A critical aspect will be to set the scene with the aim to avoid that in a few years from now the biotechnological custom manufacture will be faced with the small molecule custom manufacture situation of today.

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Dr. Marc New
Head of Corporate Business Development
Lonza Ltd.
Switzerland